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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,664	12/05/2003	Hidenobu Yaku	2003_1763A	5974

52349 7590 03/01/2007

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,664	YAKU ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *23-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 12/18/2006. Currently Claims 1-36 are pending. Claims 23-36 are withdrawn.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/18/2006 has been entered.

3. The following rejections are necessitated by amendment. Response to arguments follows.

Priority

4. Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Japan on 12/06/2002 and 08/07/2002. It is noted, however, that applicant has not filed certified translated copies of the 2002-355915 and 2003-288707 applications. Therefore, priority to the 2002-355915 and 2003-288707 applications has not been granted to the instantly pending claims.

Response to Arguments

The reply asserts that certified copies of the untranslated foreign priority documents have been submitted and that the MPEP only requires certified translations of the priority documents only to establish priority to overcome a prior art rejection over intervening art (p. 1 last paragraph and p. 2 1st paragraph). This argument has been thoroughly reviewed but is not found persuasive. 35 USC 119 Benefit of earlier filing date; right of priority (b)(3) states:

> (3) The Director may require a certified copy of the original foreign application, specification, and drawings upon which it is based, a translation if not in the English language, and such other information as the Director considers necessary. Any such certification shall be made by the foreign intellectual property authority in which the foreign application was filed and show the date of the application and of the filing of the specification and other papers.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action. This has been placed on the record to inform the applicant that in order to establish priority to the foreign documents, a translation must be presented. However, there is no declaration of interference of record.

Terminal Disclaimer

5. The terminal disclaimer filed on 6/15/2006 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US Patent Applications 11/180881 and 10/699848 has been reviewed and is accepted.

The terminal disclaimer has been recorded. The obviousness double patent rejections have been withdrawn in view of the Terminal Disclaimer.

Withdrawn Rejections

6. The rejections of the claims under 35 USC 102(b) made in section 12 of the final office action mailed 9/25/2006 and maintained in the advisory action mailed 12/06/2006 is moot in view of the amendments to the claims.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-9 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Delrio-Lafreniere et al. (Molecular Diagnosis 2001 Volume 6 p. 201).

With Regard to Claim 1, Zhou et al. teaches a method of detection of single nucleotide polymorphisms (SNPs) in a target (determining a base type) (Abstract). With regard to Claim 1a, Zhou et al. teaches a reaction solution comprising a target, SNP primers, theromostable DNA polymerase, and dNTPs (p. 4 1st column Allele-specific extension reaction). With regard to Claim 1b, Zhou et al. teaches hybridization of the primer to the target and determination of a SNP (Figure 2 p. 4). With regard to Claim 1c, Zhou et al. teaches a primer which is uncomplimentary at the third position. Zhou et al. teaches there is a complementary region adjacent to the uncomplimentary region (Figure 2 p. 4).Zhou et al. teaches detecting luminescence when the primer is extended (degree of progress (Figure 2 p. 4).

With regard to Claim 2, Zhou et al. teaches using a thermostable DNA polymerase without exonuclease activity (p. 4 1st column Allele-specific extension reaction).

With regard to Claim 3, Zhou et al. teaches the primer and the target are DNA (Abstract).

With regard to Claim 4, Zhou et al. teaches performing a PCR reaction with a forward and reverse primer (p. 4 1st paragraph).

With regard to Claim 5, Zhou et al. teaches the base difference is determined by the extension of the primer wherein no extension provides no measurable luminescence (Figure 2 p. 4).

With regard to Claim 6, Zhou et al. teaches the SNP typing can be performed by measuring pyrophosphate or by gel-based electrophoresis (Table 2 p. 9).

With regard to Claim 7, Zhou et al. teaches measuring pyrophosphate (Ppi) (Abstract). With regard to Claim 8, Zhou et al. teaches measuring the amount of Ppi generated (Figure 1). With regard to Claim 9, Zhou et al. teaches determination of the SNP (base sequence determination) and determining if the SNP is an A, G, C, or T (base type) (Figure 3 p. 5).

With regard to Claims 20 and 21, Zhou et al. teaches a method in which 16 SNPs are detected with varying size of primers (Table 2).

However, Zhou et al. does not teach a method in which the second and third positions are uncomplimentary. Zhou et al. only teaches the third position is uncomplimentary.

Delrio-Lafreniere et al. teaches the use of mismatches at the 3' end in allele-specific PCR assays for detection of wild-type and mutant alleles (Abstract). Delrio-Lafreniere et al. teaches that there is improved reaction efficiency when the penultimate base (one base adjacent to the mutant nucleotide) is mismatched (p. 202 2nd column last paragraph). Delrio-Lafreniere et al. teaches that intentional use of mismatched bases at the 3' end of the primer results in improved reaction efficiency (p. 202 2nd column last paragraph). Delrio-Lafreniere et al. teaches that nucleotides adjacent to the mutant are the most critical in the design of optimal primers (p. 203 1st paragraph). Delrio-Lafreniere et al. teaches that mismatches at the penultimate and antepenultimate bases (2nd and 3rd positions in the uncomplimentary region) on the 3' end of the primer significantly reduce preferential amplification (p. 203 1st paragraph). With regard to Claim 1, Delrio-Lafreniere et al. teaches mismatches in the primer at the antepenultimate and penultimate bases adjacent to the substitution region at the 3' end (Table 3).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the SNP detection method of Zhou et al. to include primers designed with intentional mismatches at the 3' end including mismatches at the penultimate and antepenultimate bases (2nd and 3rd positions in the uncomplimentary region) on the 3' end of the primer because Delrio-Lafreniere et al. teaches that mismatches at the penultimate and antepenultimate bases (2nd and 3rd positions in the uncomplimentary region) on the 3' end of the primer significantly reduce preferential amplification (p. 203 1st paragraph). The ordinary artisan would be

motivated to have mismatches at the penultimate and antepenultimate bases because Delrio-Lafreniere et al. teaches that these mismatches can improve the stoichiometry of the weaker reaction and yield a more balanced amplification without apparent loss of accuracy (p. 203 1st paragraph). The ordinary artisan would have been motivated to make any number of mismatches at the 3' end because Delrio-Lafreniere et al. teaches that intentionally mismatched allele specific amplification methods provide accurate results, are simple to perform, and that various intentional mismatches can be tested for optimum specificity (p. 205 2nd column , p. 201 Methods and results, p. 203 1st column 1st paragraph, Table 3, and p. 207 1st column 1st paragraph).

9. Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Delrio-Lafreniere et al. (Molecular Diagnosis 2001 Volume 6 p. 201) as applied to Claims 1-9 and 20-21 and in further view of Scopes et al. (Analytical Biochemistry 1972 Vol. 49 p. 88) and Benkoel et al. (The Journal of Histochemistry and Cytochemistry 1976 Vol. 24 p. 1194).

Zhou et al. teaches measuring ppi, however, neither Zhou et al. nor Delrio-Lafreniere et al teach the steps of converting pyrophosphoric acid into inorganic phosphoric acid.

With regard to Claim 10, Scopes et al. teaches a method of detecting the conversion of organic phosphate into inorganic phosphate (p. 88 1st paragraph). Scopes et al. teaches a method of using glyceraldehydes-3-phosphate (p. 88 1st

chemical formula). Scopes et al. teaches this gets converted into 1,3-diphosphoglycerate concomitant with the reduction of coenzyme to NADH (nicotinamide adenine dinucleotide) (p. 88). Scopes et al. teaches providing glyceraldehydes 3-phosphatedehyrogenase (p. 89 1st paragraph).

With regard to Claims 10 and 11, Benkoel et al. teaches using ferricyanide as an electron acceptor (Abstract). With regard to Claim 12, Benkoel et al. teaches determining the prices localization of various reactions in different electron transfer chains determined by using different ferricyanide concentrations and intermediate electron carriers such as diaphorase (Abstract).

Therefore it would have been prima facie obvious to one of skill in the art at the time of the invention to modify the method of Zhou et al. and Delrio-Lafreniere et al. to incorporate the method steps of pyrophosphoric conversion as taught by Scopes et al. and Benkoel et al. The ordinary artisan would have been motivated to incorporate the method steps of pyrophosphoric acid conversion as taught by Scopes et al. and Benkoel et al. in order to maximize the detection of the SNPs in the reaction. Scopes et al. teaches a rapid detection of phosphate liberation in samples (p. 88 last paragraph). The skilled artisan would be motivated to use the steps as taught by Scopes et al. to quickly detect the conversion of inorganic phosphorus in a sample. Further, Benkoel et al. teaches using copper ferrocyanide to observe electron transfer without staining (p. 11944 1st paragraph). The skilled artisan would be motivated to use both ferrocyanide and diaphorase to determine the precise localization of reactions (Abstract).

10. Claims 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Delrio-Lafreniere et al. (Molecular Diagnosis 2001 Volume 6 p. 201) as applied to Claims 1-9 and 20-21 and in further view of Bille et al. (herein referred to as Bille, 1992, Phys. Plantarum, vol. 84, pages 250-254).

Neither Zhou et al. or Delrio-Lafreniere et al. teach the measurement of pyrophosphate *specifically* where the pyrophosphate is detected by applying part of the amplification reaction to a membrane system that contains pyrophosphatase and measuring the change in H+ concentration.

Bille teaches that a quantitative relationship can be obtained between pyrophosphate concentration and a change in pH inside a vesicle membrane that contains H+-pyrophosphatase when pyrophosphate is added to a system containing vesicle membranes (claims 14, 15, and 19, see page 251, column 1, all of para 4, page 252, column 2 all of para 1, and Figures 2 and 3 of Bille). Bille teaches that the change in pH in this system is measured by a change in the absorbance of acridine orange (claims 16 and 17, see page 251, column 1, all of para 4, page 252, column 2 all of para 1, and Figures 2 and 3 of Bille). Bille also teaches that a positive current into a vacuole containing pyrophosphatase caused by a change in pH can be detected upon addition of pyrophosphate to vacuoles by the patch-clamp technique (claim 18; see page 252, column 2, all of para 4, page 253, column 1, all of para 1, and Figure 6 of Bille).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of detecting pyrophosphate in SNP detection of Zhou et al. and Delrio-Lafreniere et al. by subjecting the pyrophosphate to the system of vesicle membranes having pyrophosphatase and measuring the change in pH inside the vesicles or detecting such a pH change by the patch-clamp technique in view of the teachings of Bille for the purpose of developing a sensitive method of pyrophosphate detection in SNPs as taught by Zhou et al. and Delrio-Lafreniere et al. The ordinary artisan would have a reasonable expectation of success that using the membrane associated pyrophosphatase system with a pH sensitive dye or path-clamp method taught by Bille to measure pyrophosphate levels in the SNP detection of Zhou et al. and Delrio-Lafreniere et al. would result in a sensitive and effective measurement of pyrophosphate, as evidenced by Figures 3 and 6 of Bille, released during the extension reaction in the method taught by Zhou et al. and Delrio-Lafreniere et al. because Bille teaches a direct quantitative relationship between pyrophosphate levels and resulting pH change in vesicle membranes as measured by a pH sensitive dye or the patch-clamp technique.

11. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Delrio-Lafreniere et al. (Molecular Diagnosis 2001 Volume 6 p. 201) as applied to Claims 1-9 and 20-21 and in further view of Newton (US Patent 5525494, 06/1996).

Neither Zhou et al. or Delrio-Lafreniere et al. teach specifically labeling the primers with respective fluorescence, which are different in wavelength.

Newton teaches that allele specific amplification can be conveniently effected by labeling the primers with different fluorescent labels such as fluoroscein (green) and rhodamine (red) to allow the detection of homo- and heterozymgotes by color blending (see column 4, lines 54-64 of Newton).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of mutation detection taught by Zhou et al. and Delrio-Lafreniere et al. by labeling the primers used for primer extension with different fluorescent labels such as fluoroscein (green) and rhodamine (red) to allow the detection of homo- and heterozygotes by color blending in view of the teachings of Newton. The ordinary artisan would have been motivated to improve the method of mutation detection taught by Zhou et al. and Delrio-Lafreniere et al. by labeling the primers used for primer extension with different fluorescent labels such as fluoroscein (green) and rhodamine (red) to allow the detection of homo- and heterozygotes by color blending because Newton teaches that this labeling method allows for convenient detection of mutations by allele specific amplification.

Conclusion

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER